

## II

### DISCUSSION ON SULPHONAMIDE THERAPY IN GONORRHŒA

#### MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES

*Meeting of February 24th, 1939*

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ALTHOUGH it seems a considerable time since this subject was first introduced at a meeting of this Society, actually it is only some fifteen months ago. The rapid pace of the progress in the chemotherapy of gonorrhœa which was revealed at that meeting has not diminished. In fact the progress has even been faster in the interval ; and we have at times become a little breathless in our efforts to keep level with the extensive recent advances.

To-night we aim at a full, free and fruitful discussion on the many aspects of this new chemotherapy. There is much ground to be covered to-night and as opener of the discussion I will be brief and confine my remarks to the general aspects of sulphonamide therapy.

There are many general principles to be clarified and evaluated. We have now had some time to assess the results achieved by the more familiar sulphonamide compounds, such as sulphanilamide, Proseptasine, Solu-septasine and Uleron and probably there will be general agreement as to their value. More recently two new stars have appeared in our chemotherapeutic field. M. & B. 693 has apparently rapidly eclipsed the results of the earlier sulphonamide compounds and will, no doubt, receive full appraisal later this evening. The very recent arrival from Germany, an acetyl-sulphanilamide compound known as Albucid, a very promising youngster, will receive its London initiation later this evening.

As regards experiences with sulphonamides I would like to emphasise that this is not a discussion limited to experts. Very few of us, if any, are experts. We are all on a level feeling our way along, slowly and cautiously,

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with these newest of remedies for the oldest of diseases. Under these circumstances I would encourage you to feel that important observations may be made by those whose interest in gonorrhœa is comparatively recent as well as by those who have spent many years in its study.

When we consider sulphonamide therapy in general, it is clear that some understanding of the mechanism underlying the action of these sulphonamides is desirable for their intelligent employment in treatment. There is no need for me to dwell upon the experimental work on streptococcal and meningococcal infections which was so ably summarised for us by Dr. Buttler at our last meeting.

Although we have no laboratory animal which is easily susceptible to general gonococcal infection, nevertheless, some recent laboratory work is of considerable interest. The bactericidal action of sulphanilamide against gonococci, cultured in ascitic broth, has been demonstrated by Cohn. This bactericidal power was evident in dilutions of sulphanilamide as high as 1 in 100,000. Cohn made the important observation that strains of gonococci which were resistant to sulphanilamide in the patient were not necessarily resistant *in vitro*. In fact, some of these resistant strains were killed *in vitro* by high dilutions of sulphanilamide.

Studies by Spink and Gaston (1938) on defibrinated blood, from patients with gonorrhœa, have shown that in a considerable number of these cases during sulphanilamide therapy the bacteriolytic action of the blood was markedly increased. When the drug was discontinued the bacteriolytic titre promptly fell to normal. They considered that the amount of sulphanilamide required to maintain this high bacteriolytic titre was about 4 gm. daily. Keefer and Rantz also pointed out that the increase in anti-bacterial power of the whole blood, following sulphanilamide therapy, is independent of the formation of specific anti-bodies; for this increase was found also in normal individuals taking sulphanilamide.

But it is the clinical aspects which are our chief interest to-night. It is agreed, I have no doubt, by all who have used these compounds, that sulphonamides have attained front rank in the treatment of gonorrhœa.

There are several important principles which need your full consideration to-night. There is some question as to

when the gonococcal infection is most responsive to sulphonamide treatment. Should this treatment commence immediately the condition is evident? Does a delay of a few days or weeks confer some advantage in final result with all sulphonamides as it is reputed to do with Uleron. Is the additional therapeutic effect gained by such delay so marked that we can disregard the public health, domestic and individual personal disadvantages? My own experience is against delay even in the most recent infections. I believe that the high proportion of immediate successes, particularly with M. & B. 693, outweigh any small advantage that may be gained by delay.

Another principle on which it is desirable that we should pool our experiences, is the relative value of urethral irrigation in conjunction with chemotherapy. Many of us are reluctant to abandon irrigation. Some, because we consider that the results of the combined treatment are superior, as I do; others because the routine of daily irrigation is more likely to keep the patient under regular observation.

It has been my experience, and the experience of many others, that in order to obtain full benefit of the anti-gonococcal action of sulphonamide compounds we must use a full dosage. A low dosage, often given for several weeks, is not only likely to be useless, but may render the infection resistant to further treatment of this type. This is due, possibly, to the gonococcus itself acquiring resistance to the drug, although this explanation is not the only one. Such resistance of the infection might be due to the capacity of the liver to detoxicate a larger proportion of the compound when it is present in the blood in small amounts. In which event, presumably, a larger ration of the acetylated sulphonamide, which is therapeutically inactive, would be formed and excreted. But chemical investigations by Vest, Hill, Harrill and Pitts have failed to demonstrate any close correlation between the amount of the inactive acetyl derivative in the blood or urine and the clinical response of the disease in man.

There is some evidence to indicate that the best effect is obtained when the amount of sulphanilamide in the blood is quickly raised to a high level; 5 or more milligrammes per cent.

This can be brought about only by doses in the region of 3-5 gm. daily. In fact there is some encouragement

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from experimental work to consider using a high initial dose of the sulphonamide compound in order to rapidly attain a high blood level. This high initial dose can be followed by the more customary doses to keep up this high level.

High concentration in the blood might also be obtained by the deliberate restriction of fluids to curtail the rapid excretion of sulphonamide compound. But any interference with the usual rapid excretion of these compounds is likely to lead to intolerance. There appears to have been little consideration given to the possible importance of the amount of fluid intake during chemotherapy. In fact abundant fluids are frequently advised.

In general, I think it right to emphasise that the rationale of treatment with sulphonamides consists of full dosage over short periods with a maximum of two weeks of continuous therapy. Also the principle of giving small doses to allow toleration to be acquired is not advisable. Many of you must have experienced the difficulty of treating cases to whom small and irregular amounts of sulphonamides have been given, with little or no benefit, prior to attendance at the clinic. Such cases, in men at least, are by no means uncommon and will be possibly more frequent in the future. There are also dangers associated with inadequate treatment for there are some indications that prolonged low dosage is not immune from toxic effects.

This matter of suitable dosage is one that needs a particularly free discussion to-night not only in the treatment of gonorrhœa in the male, but in women, including pregnant women, in children of all ages in simple and complicated cases, and in metastatic conditions, such as iritis and arthritis. It is only by a generous pooling of our experiences that chemotherapy with sulphonamides will be firmly settled into the high rank which it claims.

There have been few comprehensive reports on the value of these new compounds in gonococcal arthritis, particularly in the more chronic varieties. It is possible that the sulphonamide which proves most efficient in the recent acute infections may not be so successful in the deeper-seated or chronic infections. The diffusability of a sulphonamide compound is probably as important as its anti-gonococcal action. The delayed response in

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cases of urethritis, when the follicles are infected, is probably partly due to the deficient penetration of the sulphonamide compound. This is particularly likely to be so when fibrous tissue is present. The lower incidence of folliculitis in cases treated with M. & B. 693 is conceivably due to more thorough tissue penetration.

We have been accustomed to include urinary antiseptics in the treatment of gonorrhœa for so many years that some practitioners may imagine that the anti-gonococcal action of the sulphonamides depends upon their presence in the urine. It is true that a large proportion of these compounds is excreted by the kidneys, some of it in a form which is still therapeutically active. But the well-known experimental work upon streptococcal and meningococcal infections indicates clearly that the sulphonamides act by virtue of their presence in the blood and tissue fluids. Even so, the presence of appreciable amounts of the unaltered compound in the urine may have been considered to be of value in urethritis. It is clear, however, that the marked anti-gonococcal action does not depend upon the presence of sulphonamides in the urine.

This has been demonstrated recently in a very ingenious manner by Vest, Hill, Harrill and Pitts in Baltimore. In several of their cases of gonococcal urethritis the volume of ingested fluid was so restricted that no urine was excreted during the first twelve hours of sulphanilamide treatment. Both discharge and gonococci were found to disappear just as rapidly in these cases who passed no urine as in others whose urinary excretion was normal. Their estimation of the concentration of sulphanilamide in the urethral discharge itself gave results equal to or even higher than that in the blood : although not as high as that usually encountered in the urine. These experiments would indicate that the amount of sulphanilamide in the urine is of no special value. If this be true we should expect to experience results that are equally rapid and successful in gonococcal infection whether the tissue infected is the urethra, cervix, conjunctiva or rectum. The published reports indicate a successful action in all these conditions. The value of sulphonamide therapy in metastatic infection, iritis and arthritis, has not as yet undergone full appraisal and your experiences on this aspect will be opportune.

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I have become somewhat dissatisfied with the time-honoured attitude on the rate of spread of infection to the posterior urethra. We have been accustomed for so long to note the onset of symptoms of posterior urethritis after the second week of the disease that we have been apt to consider that the infection does not reach the posterior urethra until this period. This appears to be a customary attitude in spite of the fact that there are indications that gonococci can reach the inguinal glands within a few days. Reliance on the two glass urinary test has helped to foster this belief. But now we meet with early cases in whom all signs of disease are cleared up in a few days and apparently remain clear; yet the prostatic fluid may contain an undue number of leucocytes. I look upon this prostatic leucocytosis with some apprehension, and although gonococci have rarely been found in my cases, I feel that prolonged observation and meticulous tests are necessary.

Although it is obviously the ideal to effect the disappearance of the signs and symptoms of disease at the earliest possible moment, we must not forget that our paramount objective is to render the patient permanently free from gonococci. Therefore, it is very unwise to feel too confident that the speed of apparent cessation of the disease is directly related to the speed of real cure. There are some salutary lessons to be learned from our American colleagues who report positive cultures from the prostatic fluid of cases which have exhibited rapid apparent cures.

There is a tendency, which I suppose we have all felt after our experiences with sulphonamides, particularly with M. & B. 693, to be so impressed by the rapid speed of apparent cure in large numbers of our cases, that we are carried along in this atmosphere of hustle and are tempted to reduce the number and variety of our tests and the period of observation. This is a temptation which we must resist.

The administration of sulphonamides as a prophylactic measure against gonococcal infection in man has not been so far the subject of any published report. But sooner or later, I have no doubt, these compounds will be used for prophylactic purposes, whether they are of proved value or not. It is therefore of some importance for us to bring to light any observations we may have on this aspect. I have no observations to present but some of our members in the services may have some data of interest.

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It has been reported by Cohn that sulphanilamide has a successful prophylactic action against gonococcal septicæmia in mice which can be produced by the injection of a gonococcus mucin suspension. This prophylactic action was effective when sulphanilamide was injected immediately; but delayed injection, two hours and four hours later, showed little evidence of protection. According to Hoare, mice can be protected against infection with hæmolytic streptococci by the subcutaneous injection of M. & B. 693 within the previous forty-eight hours. He suggests the use of M. & B. 693 or sulphanilamide as a protective measure in maternity cases when there is believed to be a special risk of infection with hæmolytic streptococci.

The similar use of these substances may be advisable in maternity cases when gonococcal infection is present or has been recent. If there be a widespread use of the sulphonamides for prophylaxis in maternity cases we will expect to see a decline in the number of cases of ophthalmia neonatorum. The incidence of this condition should decrease whether the prophylactic measure be directed against the gonococcus or the hæmolytic streptococcus.

My introduction of this subject has been necessarily brief, for I must make way for many other speakers. As a last word, may I say once again that it is only by a generous pooling of our experiences that this new chemotherapy will be firmly settled into the high rank which it claims.

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MR. A. J. KING, F.R.C.S. (L.C.C. Whitechapel Clinic)

THAT the sulphonamides, or at any rate some members of this group of drugs, are of value in the treatment of gonorrhœa is no longer seriously questioned; but I

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believe it to be impossible to give an accurate assessment of the value and limitations of this treatment at the present time. It is reasonable to assume that some years of experience will be required, as in the case of the treatment of syphilis with the arsphenamines, before such an estimate will be possible. It seems to me that the tendency in publications on the subject has been to claim too much and to assume too much. It is probable that many confident statements both in support of and against the use of these preparations will have to be modified after further experience and reflection. Nevertheless it is possible to say that these drugs will in the majority of cases do two things :—

Firstly, they will shorten the acute stage of gonococcal urethritis. The question of the effects on gonococcal cervicitis has not been fully studied, and it is likely to be more difficult to answer.

Secondly, they will prevent the occurrence of acute complications of the infection.

My present purpose is to put forward views on some points which are likely to be of importance in the management of cases treated with the sulphonamides, and not to give a detailed review of our experience at the Whitechapel Clinic, which would take too long. I would emphasise that the views expressed are based on preliminary impressions and will almost certainly be subject to considerable future modification, to which I hope that information gained at this meeting will contribute. These views are embodied in the replies to the following four questions.

(1) Which is the best sulphonamide preparation for the treatment of gonorrhœa having regard to the factors of therapeutic efficiency and toxicity ?

(2) At which stage in the disease should the treatment be applied ?

(3) To what extent do these drugs endanger life or health ?

(4) Do the sulphonamides cure gonorrhœa ?

(1) *Which is the best sulphonamide preparation for the treatment of gonorrhœa having regard to the factors of therapeutic efficiency and toxicity ?*

By now I think it is generally agreed that in the treatment of gonorrhœa in the male, M. & B. 693 is much more therapeutically potent than any of its rivals. We have



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now treated nearly 300 male patients suffering from acute gonorrhœa with this drug and in over 90 per cent. the infection has been controlled and the signs and symptoms have disappeared in less than three weeks. If effective dosage is given the toxic reactions are by no means negligible, but they are rarely severe enough to necessitate the termination of treatment and with perseverance most patients become tolerant to the drug. The toxic erythematous eruption of the skin which occurred at about the eighth to the tenth day in 25 (11.5 per cent.) of our first 218 male patients must, I suppose, be regarded as an indication to stop treatment if the rash is at all widespread. Our practice has been to cease administration of the drug when this occurred, but by this time clinical cure was complete in almost all of these cases. Fifty of our patients received no other treatment than the tablets but the remainder were also treated with urethro-vesical irrigations. Study of the case reports shows that the results were not in any way inferior when irrigations were withheld—a point which appears to me to be conclusive evidence of the superior efficacy of M. & B. 693, for if other sulphonamides are given in ordinary dosage it has always been essential to irrigate to obtain any proportion of good results.

As regards treatment of the female patient, there is not yet enough evidence to justify any opinion as to which is the most effective preparation. It is clear that women are more susceptible to the toxic effects of 693 even when a smaller dosage is used, and it is often necessary to terminate the treatment.

In this connection it may be of interest to mention our early experiences with the new preparation Albucid or para-aminobenzenesulphonacetamide. We have now administered this drug to 41 male patients suffering from acute gonorrhœa and the toxic effects have been very slight indeed—in most cases negligible. Eleven patients were given  $4\frac{1}{2}$  gm. of this drug daily for one week without urethral irrigations, but only two made a prompt and satisfactory clinical recovery. On the other hand, of 17 who received the same dosage over the same period combined with urethral irrigations, 15 were clinically free from infection at the end of one week. This preparation is at present under trial with the same dosage administered for fourteen days without irrigations, but pre-

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liminary assessment on this point is not yet possible. We have not yet used Albucid in the treatment of females, but in view of the absence of toxic effects in the male it should be well worth an extensive trial.

(2) *At which stage in the disease should the treatment be applied?*

The German workers who first used "Uleron" noted that their best results were obtained when the infection had been present for two weeks or more and Colonel Harrison,<sup>1</sup> possibly more with a view to provoking discussion than from deep conviction, has suggested that the sulphonamides should be withheld during the first three weeks of gonococcal infection in order to minimise the incidence of infective relapses and of default upon cessation of symptoms but before cure. Cokkinis and McElligott<sup>2</sup> have recommended that sulphanilamide should be withheld for the first eight days of infection in order to obtain better results and to lessen the incidence of relapse. From the first I have taken the view that there was no justification for such delay, and I still hold to that view for the following reasons:—

(a) Acute gonorrhœa is the clinical syndrome which results from a deep-seated suppurative process indicating that damage to the tissues is severe and that ultimate healing must be by fibrosis. Prolongation of the suppurative process increases the injury and results in more extensive fibrosis so that the infection is more likely to become chronic and the possibility of later complications due to the contraction of fibrous tissue is greater. The sulphonamides, by their anti-bacterial action, control this process and should therefore be exhibited without delay.

The case of a patient who was treated recently at the Whitechapel Clinic illustrates the importance of this point. A man of twenty-eight years, who had not previously suffered from urethritis, came for treatment three weeks after the onset of gonococcal urethritis. He was treated with M. & B. 693 without urethral irrigations and made what may be described as the usual prompt clinical recovery. Five weeks after the commencement of treatment urethroscopic examination showed a well-marked annular stricture, evidently of recent formation and yet fibrous, in front of the bulb.

(b) Despite the action of the sulphonamides it is still

the case that spread of gonococcal infection to the posterior urethra in the male is a highly undesirable complication. Metastatic infection and acute and chronic infection of the prostate may result and may prove resistant to the sulphonamides and to other treatment. During an interval in which chemotherapy is withheld posterior extension is likely to occur, but early use of the sulphonamides will in many cases prevent it. Chemotherapy is, on the whole, disappointing in the treatment of gonococcal complications, apart from epididymitis, and its function is more preventive than curative.

(c) Those who take the contrary view state that relapse is more common if there is no initial period of waiting. This may be so, although our figures do not support this view (thus, 12 of our first 200 male patients treated with M. & B. 693 suffered what appeared to be genuine relapse after apparent cure. In 6 of these treatment had been instituted during the first week of urethritis. The other 6 did not seek advice for varying periods up to three months and received no treatment for the first week or more of the infection) ; but if relapse does occur, a second course can be given after a short interval (one week) to patients who are tolerant of these drugs. I have found no reason at all to believe that patients who relapse after treatment with sulphonamides have sustained damage to or inhibition of the mechanism of immunity or have become "sulphonamide-resistant." It is true that sometimes a patient will continue to relapse in spite of repeated courses of various sulphonamides. Such cases were known in the days before the use of sulphonamides, but seem if anything to be rather less common now. The explanation is presumably that chemotherapy or any other treatment cannot help a patient unless his own tissues are prepared to make an adequate contribution.

(d) If M. & B. 693 is used there seems to be no possible justification for waiting, for the "readiness to be cured" is by no means essential. Uleron, on the other hand, has the great disadvantage that it can only be employed in short courses—too short to be effective in most cases of early acute gonorrhœa—so that relapse is very probable if the drug is used at the onset of the symptoms. In consequence there is much to be said for employing Uleron in special cases only and avoiding its use as a routine.

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### (3) *To what extent do these drugs endanger life or health?*

Our patients have not experienced toxic effects which, assuming that the necessary precautions are taken, could be described as dangerous. The dangers of sulphonamide therapy in the dosage required for the treatment of gonorrhœa have been exaggerated and are certainly far less than those resulting from the administration of arsenicals in the treatment of syphilis. Our only serious results from treatment were due to continuous dosage with Uleron before the danger of toxic polyneuritis was known. Three of our patients developed a severe form of this complication.

### (4) *Do the sulphonamides cure gonorrhœa?*

The probable truth is, of course, that they do not directly kill the gonococcus but so modify the rate of reproduction of the organism that the body defences are enabled to get the upper hand and the signs and symptoms of the infection disappear. As is well-known, the gonococcus has a resting stage in the human body when it appears to be a non-pathogenic saprophyte to the host but regains its former virulence on transference to a fresh living medium. Nothing in our work with the sulphonamides suggests that the gonococcus is deprived of this faculty of becoming a temporary saprophyte. After apparent cure with chemotherapy followed by prolonged observation and the most searching tests of cure, we still occasionally meet with relapses of gonococcal urethritis which are apparently quite genuine and not due to fresh infection. Such cases demonstrate the unreliability of the most careful tests of cure, and emphasise the importance of early chemotherapy to prevent the organism reaching the deeper tissues which are more prone to harbour symptomless infection.

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DR. ROBERT LEES (Royal Infirmary, Edinburgh) said that he had come to learn, and had been most gratified by the opening papers. He would confine his observations to M. & B. 693 which he had used exclusively since July, 1938.

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It might be of interest to members to know that in Edinburgh, adopting what was thought to be a scientific attitude, they decided to test the drug on its own merits without any adjuvant treatment. He had observed the treatment of 246 male patients, and 60 females treated in the Edinburgh Clinics under the direction of Dr. Batchelor. In addition he had reports from Dr. McGregor-Robertson, Glasgow, of cases treated with M. & B 693 and irrigation, which showed slightly better results in that there were no failures to control the infection and there was a lower incidence of complications. In Aberdeen they had tested the effects of very intensive dosage with the drug, where at present Dr. Bowie was giving an initial dose of eight tablets. This gave a high incidence of toxic effects of short duration, and very good therapeutic results. His observations, however, were still incomplete.

It would be rather tedious to give a statistical analysis of these cases, and he would emphasise the point that he did not think the time had yet arrived at which they could declare a final verdict, so that his present impressions might have to be altered in the next six months. Out of the large series of cases treated in Edinburgh with M. & B. 693 without any adjuvant treatment (the only qualification being that quite commonly a single irrigation was used after instrumental treatment), 5 per cent. did not respond clinically, they remained bacteriologically positive, and often developed complications. These cases presented a very interesting problem and much could be learnt by study and careful research into the factors underlying these apparent failures of the drug.

The next big feature was the notable increase in the number of defaulters. They were accustomed to a small percentage, but since chemotherapy had been introduced they had been faced with an increase of the number of men and women who having secured relief of their acute symptoms and signs of the disease, had not returned for discharge or been subjected to tests for cure.

The remainder—amounting to about 75 per cent.—appeared to be cured and satisfied the tests. That was his present estimate of the probable action of the drug alone. They had looked into the question of the advantages and disadvantages of irrigation in the male, and the advantage at present was in favour of the series who

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had irrigation with potassium permanganate throughout the treatment ; that series showed no failure to respond and had a slightly lower incidence of complications arising during the treatment.

The female cases responded well on the whole ; they showed definitely, as Mr. Ambrose King had mentioned, a higher incidence of toxic symptoms, but these were mainly minor symptoms. The great majority were bacteriologically uninfected by the end of the first four weeks ; very few relapsed. It was impossible at present to give figures of permanent cure because prolonged observation was necessary in females.

In complications of gonorrhœa in the male excellent results were observed. Twenty-nine cases showing gross prostatitis responded very well indeed, but after the chemotherapeutic attack persistent pus cells or leucocytes were found in the prostate fluid and the treatment was supplemented by prostatic massage and other methods. Arthritis treated by M. & B. 693 responded very well in the 4 cases treated. One case was most dramatic, a woman with an acute arthritis in the ankle joint being able to move it freely, without any limitation of movement, within three days. They had also noticed that there was not severe muscle wasting in these 4 cases of acute gonorrhœal arthritis. Acute salpingitis was also very happily influenced. Two cases of peri-urethral abscess required drainage of the abscess in addition to chemotherapy.

As far as toxæmia due to the drug was concerned, this was rarely severe, and it was only when generalised cutaneous eruptions occurred that the course of the treatment was interrupted. In most of the other cases the dose was reduced and the treatment went on. One man who had a severe toxic erythema at the end of the first treatment with M. & B. 693 acquired another gonorrhœa two months later, he was given the same drug, but this time he did not have a generalised eruption but simply suffered from headaches. This indicated that there was not an acquired cutaneous sensitisation. No dangerous toxic effect or blood dyscrasia had been observed. The drug is regarded as being extremely safe and suitable for routine use in out-patients.

The cases of bacteriological relapse were relatively few, and the speaker's personal opinion was that they

were due to an enclosed focus of infection which was not reached or only partially reached by the drug circulating in the body, and to eradicate the infection that focus must be drained or sterilised by antiseptics in addition to the taking of the tablets by mouth.

Finally, this drug seemed to bring to an acute point the necessity for adequate, and if possible, standardised tests of cure. It seemed to him amazing that with such a common disease and with so many experts they could not agree on a minimum test of cure. They must also direct attention, both administratively and practically, to methods whereby defaulters, possibly still contagious, could be brought under control. They might be faced in the future with a different type of gonorrhœa, almost impossible to diagnose, but none the less dangerous to contacts if something was not done in this direction.

DR. M. STODDART-SCOTT (General Infirmary, Leeds) said he had not come to tell members what had been done in Leeds, but he wanted to ask a question—whether anyone had found that M. & B. 693 was an abortive evacuant. He had a case of a woman eight months' pregnant and after five days' treatment she came to parturition, and he had wondered if it had anything to do with the treatment.

They had not found their defaulter rate had gone up in Leeds, and the men asked for their irrigation as well as their M. & B. 693.

One point which might be useful was the amount of treatment needed in the average case, which he thought should be the maximum rather than the minimum given in routine cases. As far as the minimum treatment was concerned he had had one case of a sailor who had four days' treatment only and went back to his ship. He was admitted to the Military Hospital in Glasgow, and had no further treatment, and on test was found to be completely cured. That might be somewhere near the minimum, but they had to find out what should be the maximum amount of treatment in the average case. The cases discharged as cured at Leeds Infirmary had on an average 12·8 days' treatment each.

DR. G. G. R. PAINTON (Bedford County Hospital) had two small clinics in Bedfordshire and had been using sulphonamide for the past eighteen months. One or two of the doctors did a test on the urine for sulphonamides

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with sodium nitrite and  $\beta$ -naphthol, and those cases who showed untoward symptoms of the drugs appeared, on very little experience, to show a low excretion rate. Those who were excreting above the normal did not show any untoward symptoms.

This brought another point, that if he used sulphonamide preparations on his patients beyond a very safe margin, they might lose their jobs, which was serious, because they could not get work again.

A third point on which he would like some information was whether it was advisable to start prostate massage at the beginning with a view to getting a flow of the prostatic secretions, and if this would help to prevent secondary complications. He thought it might.

The speaker went on to say he usually gave about 3 gm. a day to start with, for the first three days, and he found this a fairly safe dose both for the patient and himself, but the idiosyncrasy in individuals varied considerably. He would like to know whether the test he had spoken of would be helpful in small clinics to determine what was a normal rate of excretion.

MR. M. BATES (Royal Infirmary, Worcester) said he had read many papers on the treatment by sulphonamides and as a result wished to stress the importance of bacteriological findings, and not only the examination of slides, but cultures. In his experience of the use of Uleron or M. & B. 693 he had had apparent cures, and had repeated prostatic slides with as many as 1, 2, 3, 4 or 5 negatives, then on the fifth or sixth, the report came "Culture gonococcus grown." In many returns these patients would have been called cures, and he wanted to stress the vital importance of culture work as a test of cure.

COLONEL L. W. HARRISON (the Chairman), replying to Dr. Painton, remarked that his question regarding the test could probably be answered at the next meeting. As to whether one should massage the prostate in the early stages he thought he was voicing the general view in saying most certainly not.

DR. DOUGLAS J. CAMPBELL (Grimsby) said that most of his patients were fishermen who were only in port for a short time, and his greatest enemy was the ship's husbandman. A patient would come to see him, and then be told to report for duty at four o'clock the next



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morning. If the fisherman disobeyed he lost all chance of appointment to a ship for a long time, and ran the risk of being brought before the magistrate as an insubordinate sailor unless he disclosed his medical condition. So it would be appreciated that the doctor was very much biassed by the economic interests of his patients, and he had evolved, what, in Grimsby, had come to be called "the five-day cure." He had found a very high percentage of cure in men who had only five had days' treatment with M. & B. 693, and he was not claiming too high a percentage in that he never passed a man out under three months' observation.

The hard life of these fishermen must be appreciated. They went to sea for three weeks; they had an arduous life, exposed to severe weather, frequently working in ice for long periods with unsuitable food for men in their condition, very irregular rest, and certainly very inadequate facilities for self-treatment. He had been forced to issue these men (after a long talk on first attendance) with a five-day supply of tablets. The majority of the cases had shown no relapse whatsoever.

He had had to modify the treatment in a few instances of failure by issuing an irrigating outfit and a solution of hydrarg. oxycyanid., and advised them that, if after seven days there was any urethral discharge, they should irrigate until they returned at the end of the trip.

His figures now had an extraordinarily high percentage of cure. The question of alcohol had always been a debatable point in the treatment of gonorrhœa, but he could assure them that many of his lads turned up well under its influence, and even under those adverse conditions, the five-day cure was very satisfactory.

The doses he gave were as follows: to a man weighing over 11 stone he would give eight tablets, or 4 gm. a day; over 10 stone, six tablets a day, and to a man under that weight six tablets a day for the first day or two, and watch the response. He found that a man of 8 stone did not tolerate the eight tablets so well as the man of 10 stone and over.

DR. P. C. P. INGRAM (Royal Gwent Hospital, Newport) said he started with these compounds in rather a tentative way, because his patients were very much scattered, a third being seamen, another third living in the country districts and the remainder in the town, only the latter

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being able to come to him promptly if they got any untoward symptoms.

He had been looking through his case cards, and apart from being struck by the enormous clinical improvement, he thought the treatment definitely shortened the time. He had, however, only used it in about fifty cases, so that he was not really competent to speak about it yet.

There were one or two points about which he wished to be enlightened. A thing that had struck him in reading all the papers was the high percentage of toxicity, one paper giving a figure as high as 27 per cent., which seemed rather extreme. He would be interested to hear the details of a new sulphonamide which bears the reputation of being of very low toxicity.

MR. A. J. COKKINIS (St. Mary's Hospital) said it was a difficult matter to try to judge between the various sulphonamide compounds and their effects. It was a great pity that there had arisen a tendency to run one compound against others ; such a thing was essentially unethical. It was surely a point in medicine to try out all substances which were reputed to have any action in disease under fairly equal conditions, and not to pronounce judgment until sufficient clinical material had been accumulated. The question of what was sufficient material in a disease so erratic as gonorrhœa was very difficult ; perhaps 1,000 cases might be regarded as adequate. His own experience had taught him several bitter lessons, among them being late relapse after sulphonamide chemotherapy. He had seen a genuine relapse as long as eight months after complete early cure without any evidence of disease in the intervening period ; he had had a number of six-months' relapses, and quite a large number of three to four months' relapses. This was causing him great disquiet from the point of view of ultimate cure and final discharge from observation.

There were one or two points in the discussion on which he wished to say something. Dr. McElligott and he had written a paper which had been much quoted and misquoted. In that paper they claimed that sulphanilamide given in the first week of gonorrhœa produced satisfactory results. That claim he had since substantiated and he was quite prepared to prove it. At that time they had treated some 50 cases of gonorrhœa in the second week and their results were better. Since then he had had

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figures of well over 200 cases of second-week treatment, and the opinion had been amply proved that sulphanilamide given then produced much better results. The percentage of one-course cures rose from 48 to 77, and there must be a reason for it, which can only be that the second group had acquired immunity during the delay.

With M. & B. 693 the position was different. He had 60 consecutive cases treated between the first and fourth day of the disease every one of which was an initial success. He began to be alarmed and felt the drug must be inhuman, then they had four successive failures or relapses. A larger subsequent group showed similarly good early results. So far as estimated relapses were concerned he had not completed the analysis of his cases because he felt that until one could look back over a six-months' interval to see how many had come back, this could not be done satisfactorily. The cases with coincident syphilis could be followed up most adequately because of their prolonged attendance. Actually to date most of those late relapses seemed to occur in very early cases treated with sulphonamides, particularly M. & B. 693. Whether this had any bearing on delayed treatment he was not yet prepared to say. If he were forced to treat a patient with gonorrhœa in the first week he would use M. & B. 693; if in the second week he might prefer sulphanilamide; in the third week, he would consider Uleron, because that preparation showed a higher proportion of good results in third-week cases than at an earlier stage of the disease.

There must be a reason for the definite difference in the response according to the duration of the disease, and according to the drug. He believed that M. & B. 693 was the more powerful sulphonamide—he put its potency at about 1·8 more against the gonococcus than sulphanilamide, and being so powerful it was able to act even in the early stage. Sulphanilamide was less powerful, it would not cure the high percentage of first-week cases that M. & B. 693 would cure, but there is an amazing change for the better in second-week cases, owing to the development of immunity. Uleron was still weaker and therefore required a still higher degree of immunity to produce its best results.

The most important matter raised that evening had been the length of the follow-up. He did not think

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provocative tests of cure were as important as they were thought to be because he had repeatedly applied them to patients who had gone through them perfectly well and later returned as a relapse. A long period of observation was at least as important as the tests.

Another important problem was that a man who had been apparently cured might infect other people. Gonococci were left in the urethra at the end of any sulphonamide treatment, and later might come to the surface and cause a relapse. The question of discharging a patient as cured was one that had to be carefully considered.

On the question of urinary excretion of sulphonamides, this did not depend so much on the amount taken as on the fluid intake, the higher the intake the lower would be the concentration of sulphonamide in the urine.

Finally, he wished to emphasise a point he thought to be important, and that was the treatment of gonorrhœa by sulphonamide compounds by people who did not understand the principles of the treatment, and who, for instance, gave a patient with acute gonorrhœa one tablet of sulphanilamide three times a day. He had had a large number of such patients who had had anything up to six weeks' continuous treatment with one tablet three times a day and who subsequently proved absolutely resistant against high doses of both sulphanilamide and M. & B. 693. It was important that the general practitioner should know that if he was going to treat a patient with sulphonamide himself, he must do so with adequate dosage.

The period of treatment was also important, and in his opinion with sulphanilamide less than two weeks was inadequate; with M. & B. 693 in some cases a week might be adequate. But his ten-day M. & B. courses showed better results, and twelve-day courses showed the best of all, so that this probably was the right period. After the twelfth day he hesitated to continue M. & B. 693 because the incidence of toxicity had been very high.

At the adjourned meeting on March 10th, Mr. COKKINIS gave a brief summary of an analysis of 1,037 followed-up cases of male gonorrhœa treated by him with sulphanilamide or M. & B. 693. This analysis had been made hurriedly since the meeting on February 24th, and was offered to the Society as a necessarily incomplete

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statistical summary of the experience of the St. Mary's Hospital Male Clinic up to the present date. Sulphanilamide had been in use for more than eighteen months, and M. & B. 693 for about nine months. There had thus been time for a longer follow-up with the first compound : *e.g.*, 60 per cent. of the sulphanilamide cases had been followed up for three to eighteen months after clinical cure, while only 44 per cent. of the M. & B. 693 cases have had a follow-up of three months or more up to the present.

Two large groups of *first-week* cases of gonorrhœa, the first treated with sulphanilamide, and the second with M. & B. 693, gave the following approximate figures :—

TABLE I.—ANALYSIS OF FIRST-WEEK CASES

	Good Result with 1 Course	Good Result with 2 or more Courses	Ultimate Failure
	Per cent.	Per cent.	Per cent.
Sulphanilamide .	48	37	15
M. & B. 693 .	77	6	17

Two still larger groups of *second-week* cases treated with the same drugs show these approximate results :—

TABLE II.—ANALYSIS OF SECOND-WEEK CASES

	Good Result with 1 Course	Good Result with 2 or more Courses	Ultimate Failure
	Per cent.	Per cent.	Per cent.
Sulphanilamide .	77	13	10
M. & B. 693 .	85	9	6

Table I shows the undoubted superiority of M. & B. 693 in the first week of gonorrhœa. Table II at first sight suggests a slight lead for this drug over sulphanilamide even in the second week cases, but the chief conclusion to be drawn from it is the improvement in the results of both drugs when chemotherapy is delayed until the second week of the disease.

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An analysis of his *late relapses*—already 9 per cent. of the M. & B. 693 cases as against 2·3 per cent. of the longer-observed sulphanilamide cases—suggests that caution and a longer experience of the former drug are necessary before a choice is finally made between them.

He also submitted figures of subacute cases which indicated that inadequate or unsuccessful treatment with one sulphonamide compound leads to resistance to subsequent treatment with large doses of the same or of another sulphonamide compound. This resistance has frequently proved very obstinate and must be attributed to the acquirement of sulphonamide-fastness on the part of the gonococcus. It may take several weeks before this resistance disappears, and it may be necessary to wait for and even to provoke an acute relapse before the infection can finally be made to yield to sulphonamide therapy.

DR. R. FORGAN (Medical Consultant to Messrs. May & Baker) said he had had the good fortune to discuss the use of M. & B. 693 with venereologists both in London and in the provinces. He had a letter with him from Dr. Bowie, of Aberdeen, who was unable to be present and who had authorised him to ask a question on his behalf and to refer to a method of intensive dosage which he was finding effective and which was shortly to be described in the *British Medical Journal*. In three days patients received 14 to 16 gm. : 6 to 8 on the first day, 4 on the second, 4 on the third, and in some cases a smaller amount on the fourth day. On this dosage every case in the wards was found to be gonococcus-negative within ten hours. It seemed to be the best method for ensuring early and permanent cure.

The question which Dr. Bowie wished raised was on the value of the G.C.F. test in early anterior cases which cleared up under treatment within a day or two. He felt it was a waste of time carrying out a complement-fixation test on these patients. In tests of cure, which were not begun until four weeks after treatment had finished, he found in those early cases that the G.C.F. test was invariably negative.

There was an interesting analogy between the new treatment of gonorrhœa and the arsenical treatment of syphilis which, in the years immediately following the war, was not infrequently attended with early relapses owing to insufficient or unsupported dosage. It seemed

to the speaker that an entirely new phase had been entered on in the treatment of gonorrhœa. Prior to the introduction of chemotherapy all that our antiseptic treatment did was possibly to prevent the development of complications while waiting for the body to establish immunity and cure itself. Chemotherapy had cut out the natural method of cure and substituted an artificial one, and unless this was effective the last state of the patient might be worse than the first.

The contributions made to the discussion by the different observers were of great interest, but they would be of more permanent value if the Society were to form a small active chemotherapeutic committee to collect and collate the various reports and arrive at a common finding upon a new therapy in regard to which many questions still require to be answered. Should or should not irrigation be used, or vaccines be given, and if so, when? Should treatment be delayed or given as soon as possible? What should constitute the standard tests of cure in the new treatment of gonorrhœa? And with regard to the last point, he noticed that both Mr. King and Mr. Cokkinis insisted that some patients, after passing the most exacting tests of cure, relapsed several months later. Perhaps the gonococci were like old soldiers—they never die, they simply fade away. It seemed that the fading away process was not very rapid, and it was possible that devitalised gonococci might cause fresh trouble if provocative tests were undertaken too soon.

Perhaps a few remarks upon the admitted toxic effects of the drug might not be out of place. The commonest of these was gastric upset, and no method of countering this had yet been found which proved effective in every case. Sometimes less upset was caused if smaller amounts were given each time; for example, 6 separate tablets might be taken instead of 2 three times a day. The concentration of the drug in the blood fell during the night, and if the sulphonamide were regarded as a food which the body required in order to fight against the gonococcus then this might be a genuine case of night starvation. It was the custom in one hospital to waken the patients in order to give them the tablets in the middle of the night, and it had been reported to him that such patients responded more quickly than those who

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had an interval of some twelve hours in the administration of tablets. This seemed to indicate at least that a dose should be given last thing at night, although it should be remembered that sulphonamide drugs are said to interfere with sleep in some patients. Another suggestion for overcoming the gastric intolerance was to suspend powdered tablets in an emulsion of tragacanth.

In the dosage generally used in the treatment of gonorrhœa there seemed to be little risk of M. & B. 693 causing damage to the hæmopoietic system. The tendency to cyanosis was less than with sulphanilamide. One speaker had asked whether in cases of double infection (syphilis and gonorrhœa) it was desirable to give sulpharsphenamine at the same time as a sulphonamide, and the questioner was thinking of sulphur rather than of arsenic. This raised the question whether it was really necessary rigidly to reduce sulphur in the diet of patients receiving M. & B. 693. The speaker had been surprised to note a much higher incidence of intolerance at one hospital where the diet was strictly regulated than in another hospital where there were no dietary restrictions. It used to be taught that sulphur was a detoxicating agent, and it might be proved that there was no advantage, possibly even a disadvantage, in eliminating foods with a high sulphur content from the diet of patients receiving moderate doses of M. & B. 693.

On the subject of double infection, the speaker thought that arsphenamine therapy might well be withheld until forty-eight hours after stopping the sulphonamide drug, a rapidly acting bismuth preparation being used instead during the first week or so. Although the number of cases of jaundice associated with the chemotherapy of gonorrhœa was very small, it was probably unwise to administer at the same time two drugs possessing potential hepato-toxic action.

On the question of skin tolerance, at a previous lecture it had been suggested that it might be of benefit to combine ultra-violet radiation with the administration of sulphonamide drugs. While there might be experimental evidence in support of this view, it had been demonstrated clinically that such a combination was likely to result in exfoliative dermatitis, for the sulphonamide drugs are photo-sensitising agents. Most of the cases of skin tolerance seen during the past six months were



probably not of this character, and he would not be surprised if in summer time there were a large number of cases of dermatitis of the hands and face.

It was usually thought that patients with damaged kidneys tolerated these drugs well, although a reduced dosage was generally recommended. A friend of his with a staphylococcal kidney infection noticed for the first time in his life swelling of the ankles a few days after a ten-days course of M. & B. 693. The œdema subsided quickly, and after an interval the drug was resumed ; and within four days the ankles swelled again and there was complete anuria for nine hours. The condition cleared up completely on stopping the drug, but this case suggested caution in the use of sulphonamides in cases of damaged kidney.

A previous speaker had mentioned a woman who received the drug in the eighth month of pregnancy and was prematurely delivered a few days later. It was, of course, desirable that every case of this sort should be reported, but M. & B. 693 had now been given to many hundreds of pregnant women with *B. coli* and other infections, and in none of these had the drug appeared to have ecboic action.

It had been suggested that sulphanilamide and M. & B. 693 might possibly damage the testis. He mentioned this, not because he believed there was any substance in the suggestion, but because of stories that were circulating. The previous day he had heard of a patient who asked his doctor if he were going to give him M. & B. 693, and the reply was " Not unless you want to be made sterile." It seems that in a number of patients these drugs produce a transient effect upon the motility and numbers of spermatozoa, but Harkness's report in the *Lancet* of last December showed no impairment of function in 70 cases examined two months after ceasing sulphonamide treatment.

One last point—self-treatment by drugs of this sort was a thing which they all naturally deprecated. The use of these new therapeutic agents in the treatment of gonorrhœa by general practitioners unable to carry out adequate tests of cure was equally undesirable, and he hoped that some venereologist would have the courage to issue a warning to the profession in the pages of the medical journals.

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Surprise had been expressed that M. & B. 693 was not included in the poison schedule along with sulphanilamide, etc. The fact of the matter was that the Government's advisers had made a mistake in defining the chemical composition of the drugs it was intended to schedule, with the result that M. & B. 693 was exempt. He was speaking not only for himself, but also for the manufacturers of M. & B. 693 when he said that it was their wish that the drug should be sold only on medical prescription. It was to be hoped that the Ministry would make the necessary amendment in the poison rules in the near future.

DR. T. E. OSMOND (St. Thomas's Hospital). The remarks I propose to make this evening represent the views of Col. Harrison, who is too unwell to be present, as well as myself.

There seem to be rather strong differences of opinion on certain questions, notably *when* to start the treatment. The uncertainty is unfortunate because there is a danger that practitioners will not receive a clear lead from the Society on the best method of giving sulphonamide treatment. The danger is real because if we do not make clear recommendations, many practitioners will give the treatment so indifferently that there will be many relapses, possibly an increase in the incidence of gonorrhœa as a result and possibly even the development of sulphonamide-fast strains of gonococci.

From the public health point of view it is desirable to discover that method of administration which will achieve the highest percentage of cures in the shortest period of administration. It stands to reason that if the period of administration can be reduced from say two or three weeks to one a much higher proportion of patients will be carried through to completion since there will be fewer defaulters. Here the help of developed immunity may be very valuable. There is strong evidence that with Uleron, particularly, the developed immunity is not merely valuable but is essential, and in the case of sulphanilamide the evidence that older infections respond better than fresh ones is too strong to be ignored. With M. & B. 693 one may be able to achieve a high percentage of cures in early cases, but it has not yet been disproved that just as good results would be obtained in older cases with a lesser amount of the remedy.

The experimental evidence tends to show that these drugs are *bacteriostatic* rather than *bactericidal* and that cure is brought about by the patient's defensive mechanism. Some workers have objected that since one does not wait in other infections such as pneumonia or puerperal fever, why should one wait in gonorrhœa? Such an attitude discloses a complete failure to appreciate the difference between the rates at which the defensive forces of the body are mobilised. One knows for example that in gonorrhœa this is a relatively slow process. I would suggest the possibility that clinicians have arrived at their conclusions as to the time to start treatment on insufficient data. When they say they find no difference between results in cases in which gonorrhœa treatment was started very early and those when it was started later, are they sure that all the cases marked as very early were so?

I would like to see in every case note taken as to the exact day in the course of the disease when the treatment was started, whether or not the patient had had any previous attack and if practicable his gonococcal complement fixation reaction.

Some speakers have suggested that waiting is undesirable on public health grounds and Mr. King has even tried to frighten us with a "fibrosis" bogey. What danger is there to the public health in an acute gonorrhœal discharge being allowed to run on for about ten days? On the other hand, is there not great danger in a discharge stopped in the first week and allowed by the patient's neglect to relapse in the following one?

To sum up it seems highly desirable to use the minimum effective amount of drug in order to avoid side-effects. If one starts seven to ten days after the first signs have appeared there is no great risk of serious complications, especially if irrigations are given. Each case should be treated on its merits; it is highly undesirable that treatment should be machine-like.

DR. H. M. HANSHELL (Seaman's Hospital, Royal Albert Docks) said that he had used prontosil in 200 consecutive cases of gonorrhœa in man and later uleron in 300 consecutive cases. The first difference he had noted was that whereas with the prontosil group he had always to be persuading the patients to continue treatment, with Uleron he never had to do so. No patient reported that it

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upset him. He did not tell patients not to take eggs or onions but left their diet and their fancy in purges entirely to themselves ; all that he had advised was that they should try to space taking the tablets eight hourly.

Uleron was given for five days, two tablets (1 gm.) every eight hours and then stopped for five days. He soon discovered that when Uleron was stopped patients became dissatisfied, suspicious or defaulted, so in the interval he put them on acriflavine tablets. After five days of this the Uleron was repeated for another five days ; cases might have three, four or five such courses. Uleron often failed within the first ten days of infection ; the best results began after the infection was at least three weeks old. When he said it failed, it failed to produce immediate effects, but if persisted with, it eventually acted. The drug he thought had been wasted by administering it during the first ten days of infection.

The last 50 cases to be treated with Uleron were treated side by side with cases put on M. & B. 693. The superiority of M. & B. 693 was at once clear. Only a few cases on this compound reported nausea or feeling queer in the head. He had given no instructions whatever about food or drink or purges.

The dosage of M. & B. 693 was  $1\frac{1}{2}$  gm. eight hourly for five days, occasionally for seven, the patients being seen by him twice a week. At first this dosage had been reduced after five days to  $\frac{1}{2}$  gm. eight hourly for another five or seven days, but he had discontinued that practice. Now, after the initial five-day course, he gave patients acriflavine tablets and kept them under observation, repeating the full dosage of M. & B. 693 at the first suspicion of relapse.

The defaulter rate with M. & B. 693, so rapidly does it abolish symptoms and so easy, even if expensive, is it for patients to buy the drug and treat themselves, is now 60 per cent. or so of all new patients. None of his Uleron nor M. & B. 693 cases had been given any irrigations or prostatic massage. He had now treated at hospital some 300 cases with M. & B. 693 and in only one case had he noted a mild rash. He had had, however, a private patient who had recently suffered from fever, malaria parasites demonstrated, while abroad. This patient came home with gonococcal urethritis, prostatitis and arthritis ; after a week in bed on M. & B. 693,  $1\frac{1}{2}$  gm.

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eight hourly, the patient was so much better that he was allowed to go home to the care of his own doctor. Following repetition of the same dosage of M. & B. 693 for ten days the patient became very ill, with vomiting, headache, diplopia and rise of temperature. No malaria parasites were found in blood films but many undoubted myelocytes with a leucopenia of 3,000 and 20 per cent. of polymorphonuclears were observed. Complete recovery soon followed after stopping the M. & B. 693. Probably the drug in this case had adversely affected the bone marrow.

Usually in gonococcal infections in the male the results were so rapid that he thought that 90 per cent. would be cured before there was time for the drug to poison the patient.

Every tablet is stamped M. & B. 693 and the name is soon noted by the patients. They buy it for themselves, they give it to their mates and they give it to their girl friends also. All judge for themselves whether they are cured or not. All this is no small danger to the public health, especially so if it should turn out that drug-fast strains of gonococci can be produced by inadequate dosage.

DR. C. HAMILTON WILKIE (Leicester) said that he had treated over 200 acute male gonococcal cases with Uleron. The results were very satisfactory and had been published in the *British Medical Journal* in January.

These cases had received irrigations from the start as well as one, two, or three courses of Uleron tablets. Since that particular study, M. & B. 693 was being used on a large scale for male and female cases. The acute male cases had been divided into two groups, one where no irrigations were being given and another where irrigations were given concurrently with M. & B. 693. The findings would be published later. The acute gonococcal infections in the female, vulvo-vaginitis, cervicitis, and urethritis, appeared so far to be responding well to M. & B. 693, although not so well as in the case of the male patient with acute urethritis. It appeared at Leicester V.D. Centre that M. & B. 693 was superior to Uleron in many cases, although a few M. & B. 693 failures responded to Uleron.

With regard to defaulters, increase had not yet been recorded, although it was possible that this might be experienced later. Thorough tests of cure, extending

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over an increasingly long period, were more necessary than ever.

Reactions due to the drug itself had been more common in the female subject, the most severe being a marked skin eruption. One patient, after three days on M. & B. 693, had developed a desquamating dermatitis on the exposed parts, hands and face, plus marked œdema of these parts. The dermatitis cleared up in two weeks on cessation of the drug.

No anæmias or polyneuritis had, so far, been met with in Leicester following treatment with either Uleron or M. & B. 693.

DR. D. KATHLEEN BROWN (South London Hospital for Women). At the Children's Medical Home, Waddon, during the past two and a half years 70 children have received chemotherapeutic treatment for gonorrhœa. These cases have recently been reported but there are one or two points I should like to mention to-night.

The first is the question of dosage in children. After trial and error, first of too small individual doses with unsatisfactory clinical and bacteriological results and then of larger doses but continued too long and giving rise to toxic manifestations, the standard course of sulph-anilamide (prontosil album, Bayer Products Ltd., is the preparation used in the Home) is now 1.5 gm. daily for children under 4 stone in weight and 2 gm. daily for those over 4 stone. The drug is given for ten days, bringing the total course to either 15 or 20 gm. With such a course only one child has shown symptoms of intolerance. She developed an extensive morbilliform eruption twenty-four hours after completing a course of 15 gm.

In the case of M. & B. 693 again there was a period of trial and error in dosage. The first 6 cases were given 0.5 gm. three times daily for four days and showed toxic symptoms. Vomiting occurred in 4 cases and a slight pyrexia with a low polymorphonuclear count in 1 case. The standard course of M. & B. 693 now given to cases in the Home is only 0.25 gm. four times daily for four days, giving a total course of 4 gm. With these small individual doses over a short period there have been no symptoms of intolerance to the drug.

As to the time of starting treatment my impression is that the risk of failure in children is greater if sulph-anilamides are given during the first week of infection,

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but with M. & B. 693 the early acute cases respond as well as the later.

The second point which needs emphasis is the quick clinical response to treatment with the sulphonamides if the drug is going to prove effective. With M. & B. 693 the rapid disappearance of profuse purulent discharge in the acute cases is amazing, and in fact the time taken may be measured in hours. I have only had 1 case out of the 27 treated with M. & B. 693 which failed to respond at once, and this child had been given in error only .5 gm. daily for four days. But I feel convinced that if some clinical improvement is not shown within the first three days of sulphonamide treatment, it is useless to continue with that particular course.

The preparation giving the best results with my methods of treating children has undoubtedly been M. & B. 693. Apart from the shorter course of four instead of ten days' treatment, the chief advantage of M. & B. 693 over the sulphanilamides lies in the fact that it is possible to reduce still further the local treatment. In my series at the Home the vulva only was swabbed with acriflavine, 1 in 1,000 in glycerine, followed by a dermatol dusting powder for the first few days. No urethral, vaginal or rectal paintings and no irrigations have been given to any case taking M. & B. 693. When this four days' treatment is compared with the old methods involving weeks or months of general and local treatment, the change is astounding, and the tendency to relapse, that old bug-bear of gonococcal vulvo-vaginitis, is greatly reduced with sulphonamide therapy.

For the 27 cases receiving M. & B. 693 the results of treatment up to date are 7 cured, 16 probably cured, and 4 failures (15 per cent.). The period of observation varied from ten to thirty-two weeks.

I should like to make a plea for some uniformity in the duration of observation before discharging these children as cured. I still adhere to a period of six months' observation, but this has been regarded by some authorities as too long and by others as possibly too short.

It is particularly important in children to cease genital examinations at the earliest time consistent with safety. If some plan for standardising tests of cure could be made as a result of these meetings it would be most valuable.

To adult women patients I give as a rule only 14 to

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15 gm. of M. & B. 693 during seven days. Toleration of this course is good, and the vomiting which is commonly reported as a toxic symptom is absent. The results compare favourably with those obtained by larger doses.

My one complaint is that neither sulphanilamide nor M. & B. 693 affects the *Trichomonas vaginalis* infection which so frequently complicates the clinical picture of gonorrhœa in women.

DR. A. M. STUART (Royal Portsmouth Hospital). As is the general experience, I have found M. & B. 693 to be considerably more effective than sulphanilamide or Uleron. At Portsmouth all cases are given the tablets directly they are diagnosed (except in the case of Uleron), as I have always felt that the little good that may be gained by waiting for a doubtful immunity to develop is far outweighed by the risk of complications developing.

It would seem more than a little doubtful as to whether many cases of gonorrhœa ever develop a true immunity, as the C. D. T. may remain negative throughout, and immediately they have recovered they may contract the disease again.

My figures are :

Sulphanilamide	.	.	80.3 per cent. cured
Uleron	.	.	74.2     "     "
M. & B. 639	.	.	95.4     "     "

Cases are kept under observation for at least two months, generally three, and put through a fairly rigorous test of cure. M. & B. 693 has been given regularly to pregnant women and it has not brought them to parturition at any stage.

Lately I have begun to use Albucid and am so far very favourably impressed.

DR. MORNA RAWLINS (Guy's Hospital). It has given me great pleasure to listen to the stimulating and provocative papers which have been read. So far little has been said about the effect of M. & B. 693 on gonorrhœa in women and I thought a few words on their treatment might be of interest. I have a small group of 42 adult cases to report, consisting of 18 old infections, 8 recent infections of more than a week's duration and 16 recent infections of a week or less. The dosage has ranged from 7.5 to 43 gm.

My cases are not discharged as cured until they have



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been watched for six months, and only nine have been discharged as cured. All of the other cases remaining under observation have remained negative up to date. Two only have ceased to attend.

Symptoms and signs of gonorrhœa usually subside in two to three days. Films from urethra and cervix have become negative in as short a time as one and a half days. No local treatment has been given except swabbing with distilled water, and this only for the mental effect on the patient who then considers that something is really being done. The patient who received 7.5 gm. only has remained negative for two and a half months; her treatment was curtailed on account of jaundice.

In my opinion the ideal course for women is two weeks, commencing with 3 gm. daily for the first week and reducing to 2 gm. daily for the second week; the last daily dose being the largest and given late in the evening. The dose must be varied with the condition of the patient and her reaction to the drug. It must be given with food and the usual precautions *re* drugs, eggs, etc. observed.

Seven cases gave positive tests for gonococci after a course of treatment. Of these 3 were definite reinfections. Of the other 4, 2 were chronic cases and 2 were recent infections, viz. :—

(1) A chronic case. A pregnant woman who had inadequate treatment (16 gm.) owing to the development of a slight rash. This case was not due for delivery for three months, and if she had remained at my clinic would have had further treatment with M. & B. 693.

(2) Another chronic case had a course limited to 14 gm. owing to reactions. She became positive nine days later but has now been discharged as cured after a further course of 10.5 gm., which she tolerated well. This patient had previously failed on sulphanilamide treatment.

(3) A case of recent infection of seven days' duration who relapsed six and a half weeks after the first course of 35 gm. but has remained negative for four weeks after a further 24.5 gm.

(4) A case of recent infection of one month's duration who relapsed 19 days after a course which was curtailed at 14 gm. owing to a rash. This patient had later a second course of 35 gm. with a successful result and has now been discharged as cured.

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Thus in every case of relapse, except one which was transferred from my clinic, we have had a satisfactory result from a second course. Several cases showed slight intolerance to M. & B. 693. Thirteen cases suffered from rashes, usually very slight, which cleared up quickly on stopping the drug; three cases, in fact, cleared without stopping it. A few complained of headache, giddiness, nausea, or loss of appetite and 1 patient of tingling of the hands, but in no case was the reaction considered serious.

Four cases of salpingitis were treated with excellent results. Two cases with rectal gonorrhœa responded well.

M. & B. 693 in my opinion is a more potent drug than sulphanilamide for the treatment of women and is less toxic. I think that there may be an increase in the number of cases interrupting their treatment as the patients get well so rapidly, therefore I consider local treatment, such as we use, is necessary to ensure their attendance for a period of observation and testing. Has the time now come when we can reduce our period of observation of six months?

After examination of the case records of relapses I consider that however well a patient responds to this drug, she should have a full course of treatment. The majority of our patients were out-patients and there has been no difficulty in treating them as such. When clinical symptoms have not rapidly ceased we have invariably found an added *Trichomonas vaginalis* infection which is not affected by M. & B. 693 treatment.

DR. G. L. M. McELLIGOTT (St. Mary's Hospital) said that in working with Mr. Cokkinis their experience in common with everybody else was that for an immediate effect M. & B. 693 undoubtedly was, or appeared to be, a much "*stronger medicine*." The symptoms disappeared more rapidly, although, unlike Dr. Rawlins, he had found in women that 3 gm. daily were extremely toxic. In the first 25 cases, no less than 17 were unable to complete more than ten days' treatment, 7 developing urticarial rashes and the remainder severe gastro-intestinal upsets.

With regard to "fastness" to both sulphanilamide and M. & B. 693, he must admit that it was proved to his satisfaction that if small inadequate doses of either were given, and they were often given by practitioners, and

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when he said small doses he meant 1·5 gm. a day or less, the cases were as a rule most intractable and very difficult to cure.

They were getting now some extraordinarily disquieting remote relapses after tests of cure of cases treated originally with sulphanilamide and M. & B. 693.

He was sorry that some other people did not try the principle recommended originally, of waiting a short time before treating cases with sulphanilamide, because the results were to his mind infinitely better than in the first week cases, which were depressingly bad. He agreed with everything Dr. Osmond had said on that point and he felt that when they really got to the bottom of this question there would be two methods of treating gonorrhœa with the sulphonamide compounds. One would be Dr. Bowie's method of giving the drug in very large doses in the early stage, and the other would be to wait until the body had acquired enough immunity to help along lesser doses of the drug.

With M. & B. 693 that did not appear to be so necessary because it was a much more powerful drug, but he thought that the same principle would hold good and even better results would be obtained with M. & B. 693 if it was used either as Dr. Bowie had used it, or as he and Mr. Cokkinis had originally used sulphanilamide. At present, they were giving Dr. Lloyd's method a full and exhaustive trial, and so far found it satisfactory.

He would like to mention a case he had last year of a healthy man who was receiving sulphonamide treatment for gonorrhœa. At the beginning of the second week he developed a generalised morbilliform rash with some œdema of the face. A blood count was taken at once and showed 19,000 lymphocytes of an immature type, and the pathologist suspected acute lymphatic leukæmia. The man refused admission to hospital because he did not want to lose work. Two days later the rash had disappeared, the blood count on repetition was perfectly normal and had the leukocytes one would expect at that stage of the gonorrhœa. The only explanation he could offer—and he would like to know what others thought—was that the bone marrow and lymphatic glands shared in the urticaria with the skin and that there had been a sudden diapedesis of immature cells into the circulation, and as soon as the toxic effect of the drug had ceased,

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owing to the drug being excreted, these immature cells had been got rid of in the ordinary way.

Another case which he had met with was that of a child two years old who had an acute meningitis. The cerebrospinal fluid showed 1,000 polymorphonuclear leukocytes per cubic centimetre. A pure culture of Pfeiffer's so-called influenza bacillus was grown from the cerebrospinal fluid. The child was treated with M. & B. 693, he had forgotten the exact dosage, but it was on the lines on which Dr. Kathleen Brown treated her cases of vulvo-vaginitis, a fairly adequate dose. The temperature subsided and the cerebrospinal fluid became less cloudy and eventually a sterile culture was grown. After a short course the symptoms recurred, and there was exactly the same picture again with Pfeiffer's bacillus in the cerebrospinal fluid. More M. & B. 693 was administered, and treatment was suspended on the fourth day owing to severe hæmaturia. A temporary cure was again followed by a relapse and the patient was eventually cured with a third course lasting seven days. When the drug was finally stopped the hæmaturia disappeared.

DR. D. NABARRO (Hospital for Sick Children, Great Ormond Street), Chairman, said that the discussion had been most interesting and illuminating. This group of drugs, and certainly M. & B. 693, seemed to have initiated an entirely new era in the treatment of gonococcal infections. Personally, he could speak only of infections in children. Those of them who could throw their minds back fifteen or twenty years when they had to treat vulvo-vaginitis in little girls, could remember how lengthy the treatment had to be, extending for four or six months, and in the more resistant cases ten or twelve months or even longer. But when it came to these sulphonamides, and particularly M. & B. 693, something really dramatic occurred in the treatment of gonococcal vulvo-vaginitis. He had one case of a child of nine who was brought to the clinic on a Friday afternoon with the typical discharge, which had been present for nearly a week. He took smears and made a culture and the gonococcus grew well. The child was given a tablet of M. & B. 693 on the Friday afternoon and a tablet on the Saturday morning—that is, a total of 1 gm. of M. & B. 693—and that was now three months ago, and she was perfectly well and all subsequent films and cultures as well as the G.F.T., were negative.

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He had not himself had a large series of cases treated by this preparation, but his dosage had varied from 1 gm. in the case just mentioned to 14.25 gm. which he gave to another child on nine consecutive days. The gonococci were present in that case on the sixth day after he started treatment, but the findings were negative thereafter. The only children who had exhibited any toxic symptoms were two young children, to whom he gave  $2\frac{1}{4}$  and  $3\frac{1}{4}$  gm. respectively. He had tried the drug in a few cases of non-gonococcal vulvo-vaginitis due to streptococci, and although the symptoms disappeared the organisms did not seem to be so responsive to the treatment. One wondered how 1 gm. given by mouth could clear away the gonococci in the vagina.

Dr. Forgan had suggested that a chemotherapeutic sub-committee should be established in the Society. He personally thought that was a wise and sound suggestion. It might work particularly on the various points which Dr. Lloyd had raised.

He thanked Dr. Lloyd and Mr. Ambrose King for their opening addresses.

DR. V. E. LLOYD (in reply). It now falls to my lot to attempt to crystallise the general impressions that have resulted from our discussion to-day and at our meeting here two weeks ago.

In general our anticipations have been well fulfilled for we are all agreed that sulphonamide therapy has effected a very marked step forward in the treatment of gonorrhœa. It is clear to all of us that this therapy is no mere fashionable and evanescent line of treatment but is a firmly established advance, probably applicable to all the manifestations of gonococcal infection. The beneficial effects most clearly established and most striking are those evident in recent infections in the male. There is also considerable evidence of rapid and apparently curative action in gonococcal infection in women and children.

The story that begins with sulphanilamide and passes on to Prontosil soluble, Proseptasine, Uleron and M. & B. 693 is a story of vision, industry, progression and achievement. It has been said in the past, often enough,

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that the amount of productive research in gonorrhœa was depressingly small considering the number and size of the clinics and laboratories dealing with venereal disease. Like many others I have smarted from such stings in the past and now I feel that some praise is due to the many workers in this field for their quick and ready response to develop and establish new ideas in treatment. This great and widespread response is sufficient answer I feel to those who in the past have criticised the volume and scope of research work in gonorrhœa.

It is also evident that this most rapid advance in our speciality has been dependent not only on laboratory research but on extensive clinical research. The clinicians who have patiently dealt with gonococcal infections by all the available older methods have not been found wanting when the opportunity came to develop their therapy along new lines, and this they have done with enthusiasm coupled with caution and judgment.

There appears to be little doubt that the effective action of sulphonamides in gonorrhœa, as in other infections, is mainly achieved in the first day or so of their administration. It is equally apparent that some gonococci may survive the immediate action of the sulphonamides and be responsible for a relapse if the treatment is omitted after a few days. As regards dosage we are not yet likely to agree to a rigid schedule with any one of the sulphonamides. There is, however, a clear tendency to advise a decreasing dosage with the maximum amount restricted to the first few days of treatment ; and to continue treatment of a less intensive nature for at least ten to fourteen days however prompt the initial response of the disease may have been ; and to delegate further treatment if required to a second course after a period of rest.

Several members have referred to the advisability of spacing the daily dosage so that some of the compound is taken at night. There is no doubt that the effective action of these sulphonamides depends upon the maintenance of a high blood level by day and by night. Wide spacing of the daily doses is more efficient than the customary method of taking the tablets after the three main meals of the day.

It is also evident whatever sulphonamide compound is employed that some gonococcal infections are resistant.

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Our further progress will arise, I think, from careful observations upon our failures rather than upon our successes. These resistant and relapsing cases are worthy of intensive study. What is the reaction of the tissues to the infection in these resistant and latent cases following sulphonamide therapy? Does the tissue reaction differ in type or extent from that in untreated cases? Does the virulence or vitality of the remaining organisms remain unaltered or undergo some modification? These queries and many others are awaiting investigation and much can be done by clinical observation.

Some uneasiness has been expressed as to the value of provocative and other tests for cure in sulphonamide treated cases. There have been several pleas for a standardised series of tests of cure in gonorrhœa. It is very remarkable that no comprehensive reports on the relative value of the various tests in use have been published and this omission testifies to the extreme difficulty in ascertaining if and when the infection has been finally overcome. Such studies are urgently needed as part of our present campaign. We all use a variety of tests but very few of us I imagine are prepared to attach a figure of relative merit to the individual tests.

Some time ago I kept special records of apparently cured cases of gonorrhœa in men who relapsed after provocative tests, such as the injection of a large dose of a vaccine, the use of metal bougies, the instillation of silver nitrate and the ingestion of alcohol.

I encountered more relapses following the provocative effect of silver nitrate than after any of the other procedures and I still consider this test to be the most efficient. Yet, I understand, this test is used far less to-day than formerly.

One of the most striking features of sulphonamide therapy is the marked reduction in the incidence of gonococcal complications. This feature has not been stressed very forcibly at this meeting, but when we look back upon the amount of ill health, both mental and physical, produced by the many complications of gonorrhœa in the past we realise that this reduction of complications is a very notable step forwards in the campaign against gonorrhœa.

As regards the various sulphonamide compounds in use at the present time, M. & B. 693 (2 sulphanilyl-amino-

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pyridine) appears to be the most efficient in the prevention of gonococcal complications and it is the general opinion that this compound is the most potent anti-gonococcal agent now available. On the question of delay in the institution of treatment, which has been recommended with Uleron and to a less extent with sulphanilamide, it appears that those who have used M. & B. 693 are in agreement that delay in recent infections is unnecessary and inadvisable.

The importance of adjuvant treatment such as irrigation in urethritis and vaccine therapy appears to have declined since favourable reports have been made on cases treated with chemotherapy alone. But many members of this Society evidently still consider that a combination of chemotherapy with irrigations gives the best results. This feature is evident with the most recent sulphonamide, known as Albucid, which in Mr. King's hands gave better results when associated with irrigation treatment. My short experience of Albucid in the treatment of men also demonstrates considerable efficiency when used in conjunction with irrigations with permanganate solutions. Vonkennel and Korth, who obtained excellent results with Albucid in Germany, used both vaccine therapy and urethral irrigations for the first week of treatment and commenced Albucid in the second week.

The tolerance of this new compound is stated to be excellent, but mild toxic effects are not entirely absent for I have noted a granulocytopenia of mild degree in 2 cases receiving  $4\frac{1}{2}$  gm. daily. Nausea and headache was also a complaint in one case. The reputation of this compound for perfect tolerance led me to advise its use in the case of an experienced airman who subsequently was called upon for emergency flying duties. His flying experience, whilst under the effect of Albucid, led to his statement that no one should act as pilot when taking this drug. This dictum obviously applies to all sulphonamides.

Some apprehension has been expressed concerning a latent stage of gonococcal infection that may occur in men, and presumably in women, after the first initial onslaught of sulphonamide chemotherapy. In this state, which may with justification be called "the fools paradise," early default from treatment has been feared by many of us and appears to be a serious factor in some



clinics. One wonders how many of these defaulters will be responsible for further dissemination of infection and what effect an increase of early defaulters will have upon the general incidence of this disease. No doubt a proportion of these early defaulters are cured but it is certain that some are a danger to the community. The more dangerous cases are those in whom the organisms remain latent and show little or no signs of their presence. Whether many cases remain in this latent stage for long appears to be unknown. My own experience has been that most of such cases show obvious signs of relapse within a brief period. Yet several speakers have commented upon the occurrence of long period relapses.

The successful action of sulphonamides has so markedly reduced the period of active treatment that, as regards the clinics, the number of attendances required for each case has been reduced. At Guy's Hospital the number of attendances of cases of gonorrhœa has been reduced by one-third in the last year. This decrease, which is probably manifest in the annual figures of all clinics using sulphonamides, might encourage the controlling authorities to contemplate an early curtailment in the services available in gonorrhœa clinics. This short-sighted policy I am certain would be a grave mistake. This is no suitable time for the reduction of medical services available for gonorrhœa. It is a time for maximum concentration on a successful treatment; for further intensive laboratory and clinical research; for a more intensive campaign of advertisement and propaganda on the part of the controlling authorities. The public health outlook should be one of active progression, to follow hard on the heels of our rapid clinical advances. Very rarely has any campaign been won with the first victory. There are some who feel that the story of gonorrhœa may yet have a chapter comparable to the first flush of enthusiasm which characterised the salvarsan treatment of syphilis.

It is therefore our duty and our privilege to establish the permanent value and limitations of this new chemotherapy by further meticulous and unremitting toil in laboratory and clinic.